The Examiner rejected claims 1 and 7 under 35 USC 102 (b) as being anticipated by US 5,585,112 issued to Unger and US 5,536,490 issued to Klaveness. In addition, claims 1 through 13 were rejected under 35 USC 103(a) as being unpatentable over Klaveness or Unger. Applicant requests reconsideration of the claims. The references, viewed individually or in combination, do not anticipate, teach or suggest the claimed subject matter within the meaning of 35 U.S.C. §§ 102(b) or 103(a).

Klaveness teaches that amphiphiles must be assembled around a gas to form a microbubble that is then cross-linked to "fix" the shell for stability. *See, e.g.,* column 1, lines 50 *et. seq.* Klaveness therefore teaches away from use of simple mixed length amphiphiles in forming microbubbles for ultrasound contrast by necessitating the use of polymerization or cross-linking of the shell forming material. In contrast, under the teaching of the present invention, cross-linking is unnecessary because of the unique "shell" layer formed over the gas by the hydrophobic groups of different lengths. The physical nature of the assembly necessitates that the longer chains fold in and overlap in the gas phase constituting an inner layer obliquely aligned relative to the main assembly. *See, e.g.,* Figure 1. This greatly improves stability as measured by shelf-life and *in vivo* half-life compared to similar formulations that are not cross-linked and having equal carbon length chains. It also provides for a unique acoustic response at a given ultrasound frequency manifested by decreased attenuation (scattering and image loss) without diminishing backscatter (reflectance and contrast). The response is very sensitive to changes in surrounding pressure. Cross-linking is not necessary and is considered undesirable for a number of reasons, including the long metabolic decay and elimination, liver uptake, uncertain toxicity of various sized particulates from polymer microbubble decay and less dynamic acoustical response caused by the dampened resonance of a less compliant shell.

Klaveness discloses amphiphiles of the sort shown in formula II of his patent, at column 5, line 51. B is defined as a group capable of polymerization or cross-linking when either X or R^{10} is not capable of polymerization or cross-linking. Under the teaching of the present invention however, polymerizable/cross-linked groups such as B, X and R^{10} are not present or necessary. Klaveness further discloses the use of preformed polymers, specifically PEG derivatives, as a special case of formula II (line 45, column 6). If a hydrophilic polymer, PEG, is part of formula II, and if X or R^{10} is not polymerizable or cross-linkable

then B must present as a group capable of such (refer to example 7, column 15, lines 6 through 27). The amphiphiles described by Klaveness are therefore outside the scope of the present invention. Since the present invention does not use polymeric or cross-linkable amphiphiles, the use of initiators such as described by Klaveness (*See* Table 1, column 19, lines 10-59) in the preparation of microbubbles by sonication is totally avoided.

Unger teaches a method of preparing gas and gaseous precursor-filled microspheres which must be "activated" by some means to produce gas-filled liposomes. Under the teachings of the present invention, the microbubbles are produced directly and are stable for extended storage.

The shell design as taught by Unger differs from that of the present invention. Unger incorporates a gas within a multilamellar shell (gas-filled liposomes). Stability in this type of formulation is provided by the multiple layers of "multipodal" amphiphilic compounds assembled by having the hydrophobic units of each layer in contact and intermingled with the preceding layer. It is well known that liposomes are commonly constructed of bipodal amphiphiles (generally phospholipids); whereas, single-chained amphiphiles as major wall forming components rarely assemble into such structures. Although multi-chained amphiphiles connected to hydrophilic polymers are optional components in the present invention, their concentration are comparatively very low given the high molecular weights; therefore, their presence could not typically support liposome formation. Further, the present invention demonstrates that a multilamellar wall is not necessary for good agent stability.

Unger teaches away from the use of a simple monolayer of mixed length amphiphiles stabilizing a gas for the preparation of an ultrasound contrast agent and instead teaches the use of a multi-layer shell around a gas precursor. *See, e.g.,* the depiction on page 1 as well as Figs. 9 and 10.

Moreover, specialized procedures and equipment for preparing the precursor liposomes are given by Unger in Fig. 1. Such methodology is obviated by the present invention. The gas-filled liposomes once formed require a filtration step, as depicted in Fig 4. No filtration is necessary under the teachings of the present invention. Further, the acoustic performance of gas-filled lipsomes is different than that exhibited by the microbubbles of the present invention. The acoustic performance of Unger's liposomal agents as reported in the literature is similar to protein shell microbubbles. *In vitro*

ultrasound measurements of microbubbles of the present invention compared to protein shell microbubbles show dramatic differences including a reversible pressure mediated shift in acoustic response, as demonstrated in Table 1. Thus, the difference in ultrasonic response of gas-filled liposomes to the microbubbles of the present invention is a direct measure of the difference in shell assemblies.

CONCLUSION

For all of the foregoing reasons Applicant requests reconsideration of the rejections applied under 35 USC §§ 102(b) and 103(a) against the claims.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this Amendment (together with any documents referenced therein) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: December 20, 2002

Barbara A. Krisch

VERSION WITH MARKINGS TO SHOW CHANGES

IN THE CLAIMS:

Claim 7 has been amended as follows:

7. A method for obtaining an ultrasound contrast image of body tissue comprising:

administering [inserting] a composition useful as an ultrasound contrast agent comprising microbubbles encapsulating a gas within a shell made from a blend of bipolar compounds having inter-molecular hydrophobic regions of mixed carbon chain length into a body; and taking an ultrasound image of the desired tissue.